Tbx20 regulates a genetic program essential to adult mouse cardiomyocyte function.

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Public Summary:
Human mutations in or variants of TBX20 are associated with congenital heart disease, cardiomyopathy, and arrhythmias. To investigate whether cardiac disease in patients with these conditions results from an embryonic or ongoing requirement for Tbx20 in myocardium, we ablated Tbx20 specifically in adult cardiomyocytes in mice. This ablation resulted in the onset of severe cardiomyopathy accompanied by arrhythmias, with death ensuing within 1 to 2 weeks of Tbx20 ablation. Accounting for this dramatic phenotype, we identified molecular signatures that posit Tbx20 as a central integrator of a genetic program that maintains cardiomyocyte function in the adult heart. Expression of a number of genes encoding critical transcription factors, ion channels, and cytoskeletal/myofibrillar proteins was downregulated consequent to loss of Tbx20. Genome-wide ChIP analysis of Tbx20-binding regions in the adult heart revealed that many of these genes were direct downstream targets of Tbx20 and uncovered a previously undescribed DNA-binding site for Tbx20. Bioinformatics and in vivo functional analyses revealed a cohort of transcription factors that, working with Tbx20, integrated multiple environmental signals to maintain ion channel gene expression in the adult heart. Our data provide insight into the mechanisms by which mutations in TBX20 cause adult heart disease in humans.

Scientific Abstract:
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